EXHIBIT DD

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF WEST VIRGINIA

CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327 MDL 2327** **JOSEPH R. GOODWIN U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 1 Cases*	

Expert Report of Roger McLendon, M.D.

I. BACKGROUND AND QUALIFICATIONS

I am board certified in Anatomic Pathology and Neuropathology, having trained at Duke University Hospital between July 1983 until June 1987, passing my boards in May, 1987. I have been on faculty at Duke since January 1992 with a practice that has been largely confined to surgical and autopsy neuropathology. I have been a member of the American Board of Pathology Neuropathology Test Development and Advisory Committee since 1998 and am on the editorial boards of the Journal of Neuropathology and Experimental Neurology, Neuropathology and Applied Neurobiology, Archives of Pathology and Laboratory Medicine (Sectional Editor), Clinical Neuropathology and Neuro-oncology. A more complete list of my academic publications and accomplishments can be obtained from my curriculum vitae (Exhibit A). In my practice, I routinely review sural nerves for medical diseases as well as surgical

specimens for traumatic neuromas, nerve tumors, nerve roots resected for pain, and fila terminale resected for tethered cord syndromes, among other specimens where evaluation of peripheral nerves is an ancillary aspect of the evaluation.

In preparing my report, I have reviewed Dr. Iakovlev's report dated January 29, 2016, Dr. Iakovlev's report dated August 24, 2015, and several publications authored by Dr. Iakovlev and others.

I reserve the opportunity to supplement this report and my opinions upon my review of any pathology slides recently provided by counsel for the plaintiffs and my review of any additional depositions and other discovery conducted in this matter.

II. OBSERVATIONS, ANALYSIS, AND OPINIONS

I have formed the following opinions to a reasonable degree of medical certainty:

1) Dr. Iakovlev is not a fellowship trained, board certified neuropathologist.
2) As described below, Dr. Iakovlev lacks a fundamental understanding of the physiologic implications distinguishing nerve fiber locations and nerve receptor locations. In the absence of understanding the anatomic locations of the nerve receptors, the location of the nerves in Dr. Iakovlev's photomicrographs and report has no significance with regards to pain causation.
3) As described below, Dr. Iakovlev lacks a fundamental understanding regarding the role of ganglia in mediating autonomic motor signals to end organs (bladder, colon, glands, blood vessels, etc) and that ganglia have no role whatsoever in processing pain signals from the pelvic region.
4) As described below, Dr. Iakovlev lacks a fundamental understanding of the stains he is using to demonstrate nerve fiber locations, confusing the presence of large diameter myelinated fibers within fascicles (as shown by his S100 stains) as being representative of the location of small diameter, unmyelinated, single fibers in the pelvis.
5) The studies published by Dr. Iakovlev and colleagues represent merely descriptive studies of the nerves, fibrous tissues, fatty changes, and appearances of polypropylene in

the mesh specimens implanted for stress urinary incontinence and removed for various reasons.

6) Statements related to pain pathogenesis in Dr. Iakovlev's report lack scientific rigor given the absence of comparable studies in tissue removed from females who lacked pain and felt symptomatic relief of stress incontinence.
7) Statements related to pain pathogenesis fail to explain if the pain is related to the mesh or to an unnoted complication of the operative procedure (Vervest et al. 2006). (Svenningsen et al. 2014)
8) Statements relating pain pathogenesis to fibrous tissue about the mesh fail to explain why published studies reporting microscopic findings of post-operative meshes reveal a normal number and density of nerve fibers in the tissue. (Bendavid R 2014)
9) Clearly, Dr. Iakovlev's article on post-herniorrhaphy does not apply to this analysis as the authors note that in those patients the surgery was complicated by voluminous and complex repairs and that pain was significantly associated with either open repair versus laparoscopic repair. However, most disturbing in this article was Dr. Iakovlev's analysis of nerve fibers. The article indicates that the authors believe that whole fascicles can grow into the mesh pores. This is an anatomic impossibility known for almost 100 years. Further, it is well-know that traumatic neuromas will artifactually interfere with nerve counts as individual axons grow out of fascicles and disperse to make the nerves more apparent. In this article, there is no accommodation for this artefactual increase in nerve counts. Indeed, it clearly appears that these nerve counts account for the difference attributed to the painful meshes. Not accounted for in this regard is the impact of the surgical technique in causing the traumatic neuromas rather than any passive effect of the mesh/nerve interaction.
10) Statements relating pain pathogenesis to increased inflammatory infiltrates fail to reconcile their findings with the findings of Elmer and colleagues who found fewer inflammatory cells, fewer fibroblasts, and unchanged numbers of granulocytes, lymphocytes and monocytes in pre-operative transvaginal biopsies than in their subsequent post-implantation biopsies. (Elmer et al. 2009)
11) Statements related to inflammatory findings being always found are belied by arguments in which only fibrous tissue is found about the polypropylene material. Furthermore,

statements related to inflammation being invariably present are denied by the Hill study (Hill et al. 2015) in which no inflammation was noted in 9.2% of cases as well as by Smith et al. (Smith et al. 2013) in which the terms inflammation and giant cell reaction were used in only 10.4% and 18.8% surgical pathology reports respectively. Furthermore, pig model studies have demonstrated that polypropylene meshes have the lowest inflammation score among all mesh materials tested, characterized as "weak lymphocyte and macrophage reactions." (Boulanger L 2006)

12) Statements related to inflammation being responsible for pain are denied by the publication of Hill et al. (Hill et al. 2015)
13) Statements suggesting that fibrous tissue results in traction, and therefore pain, are not supported by any findings indicating that pain receptors are found in the tissue, their distribution or that the nerves are pain-transmitting nerves rather than autonomic nerves.
14) Statements suggesting nerves between mucosa and fibrous tissue mediate pain are not supported by any findings that the nerves have receptors in the region or transmit pain rather than being autonomic motor nerves.
15) Statements suggesting that ganglia entrapped in fibrous tissue are non-functioning are not supported by any physiologic data. Any implication that ganglia mediate pain is false.
16) "Some patients fitted with a SMUS report pain that is associated with specific movements or activities. The observation of interlocking of the mesh and striated muscle – resulting in muscle contraction and traction on entrapped nerves – offers a plausible hypothesis to explain this phenomenon in patients fitted with TOT slings." (Blaivas et al. 2015). It goes without saying that a hypothesis is not a fact, but needs rigorous testing scientifically. Using the standard, "more likely than not", this hypothesis fails as it does not examine the number and distribution of nerve receptors not does it examine other potential causes of pain such as the pain that is associated with psychogenic pain, the pain associated with healing after passing, but not leaving, a foreign body through this part of the body, etc.
17) Any implication that nerves "grow" into a "mesh scar plate" by way of fascicles is false and has been known to be false since the earliest histologic studies of the nervous system (Ramon Y Cajal, 1959)

18) Any implication that nerve fascicles as shown by H&E stain represent functioning nerves is false given that not only nerves reside in fascicles but also blood vessels, Schwann cells, macrophages, and perineurial cells, all of which may remain long after the functional axonal fiber has degenerated while maintaining the microscopic appearance of a normal nerve fascicle.

19) Nerve fibers are the longest cells in the human body, some of which extend from the spinal cord to the toes. In order for these fibers to function, they must be able to be distorted across joints, bones, and muscles thousands of times a day.

I have formed the following opinions to a reasonable degree of medical certainty regarding the photographs supplied by Dr. Iakovlev:

Figure set 3a. "Nerves within the mesh spaces (note distortion of the nerve in the upper panel), H&E, 20x and 2.5x"

McLendon response: The "nerve" highlighted by arrows in the figures represents bundles of nerve fascicle-associated cells that are pushed aside by a polypropylene thread. The nerve, by H&E stain, appears histologically to be normal and intact. No stains are provided to allow examination of the presence or absence of axons in the fascicle. There is no evidence of a pathological reaction by the nerve to the thread.

Figure set 3b. "Nerves severely distorted by the mesh fibers, H&E, 20x."

McLendon response: In this figure, there appears to be wrapping of fascicle cells about a polypropylene thread. No stain or other evidence is provided that indicates viable axons are still present in the fascicle. There is no pathologic reaction of the nerve fiber to indicate that it is regenerating.

Figure set 3c. "Nerves severely distorted by the mesh fibers, H&E, 20x."

McLendon response: There are two nerves on either side of a polypropylene thread. There is no evidence that they are the same nerve.

Figure set 3d. "Nerves severely damaged by the mesh fibers, H&E, 20x. The nerve in the upper panel is nearly transected longitudinally. The nerve in the lower panel has separation of the fascicles in the scar tissue = traumatic neuroma."

McLendon response: The nerve in the upper panel is associated with a ganglion and is clearly an autonomic motor nerve that provides no pain sensation. The arrow purporting to demonstrate "mesh transmigration through a nerve" in actuality shows a thin delicate nerve fascicle being draped around a polypropylene thread without a pathologic reaction of regeneration. The tissue in the lower panels shows no evidence of regeneration; rather it is wrapped by a few perineurial cells along the outer periphery of the nerve fascicle. No axon stains are provided to determine if the axons are present in the nerve.

Figure set 3e. "Deformation of the nerves and formation of traumatic neuromata, S100, 4x and 10x."

McLendon response: Despite the low power magnification, the tissue in the upper panel appears to show that the outer sheath of the nerve fascicle has been pulled out resulting in the S100 positive nerve cell elements to be pulled apart during surgery. No axonal stain is provided to determine if any axons are involved in the reaction. There is no evidence of a "traumatic neuroma" in this photograph. In the lower panel, it appears that a foreign body giant cell reaction is around a polypropylene thread and S100 positive neural cellular elements are adjacent to the reaction. No axon stains are provided to determine if the axons are present in the nerve.

Figure set 3f. "Deformation of the nerves, S100, 20x and 10x."

McLendon response: In the upper panel, it appears that a thin delicate nerve fascicle wraps about a polypropylene thread, exhibiting no pathologic reaction. No axon stains are provided to determine if the axons are present in the nerve. In the lower panels, a thin delicate nerve fiber (approximately a quarter of a millimeter in diameter) is draped around a collection of polypropylene threads without showing a pathologic reaction. No axon stains are provided to determine if the axons are present in the nerve.

Figure set 3g. "Severe deformation of the nerves by the mesh fibers, S100, 20x. The nerve in the lower panel has separation of the fascicles as occurs in traumatic neuromata."

McLendon response: The nerves in both the upper panels are associated with ganglia and are clearly autonomic motor nerves that provide no pain sensation. The nerves in both the upper and lower panels reveal fascicles draped about polypropylene threads with no obvious pathologic reactions. Specifically, the fascicle in the lower panel shows no evidence of the whorling and proliferation of individual regenerating nerve fibers seen in a traumatic neuroma.

Figure set 3h." Degeneration of affected nerves, S100, 20x, Degenerative type of changes in peripheral nerves, Renaut bodies have been associated with chronic nerve trauma and entrapment [567-570]."

McLendon response: The nerve fascicle in the upper panel demonstrates a nerve fascicle with its fiber elements pulled apart, not "degenerating". In the absence of being able to see where this nerve is in relation to the surgical margin, it is not clear if this finding is normal or related to the surgical procedure involved in removing the mesh. Regardless, the nerve fascicle elements before and after the area pointed out by the arrow are well staining by the S100 stain. No axonal stain is provided to determine if there is axonal loss in the fascicle. Renaut bodies are not features of degeneration. While they have been associated with entrapment, they are most commonly encountered in normal peripheral nerves.

Figure set 4a. "Neural ganglia, H&E, 40x and 4x."
Figure set 4b. "Neural ganglion affected by the mesh, H&E, 20x."
Figure set 4c. "Neural ganglion affected by the mesh, H&E, 20x."
Figure set 4d. "Neural ganglion affected by the mesh, H&E, 20x"
Figure set 4e. "Neural ganglion affected by the mesh, H&E, 20x"

McLendon response to 4a through 4e: Neural ganglia are a normal and plentiful component of the autonomic motor nervous system in the human pelvis and, in no way, mediate pain. Dr. Iakovlev's point in this set of pictures is unknown.

Figure set 5. "Innervation of mucosa overlying the mesh, s100, 4x."

McLendon response: This set of pictures of an S100 stain demonstrates small nerve fascicles, not individual twigs, underlying mucosa. It is well known that the vaginal submucosa is heavily innervated by autonomic motor nerves that provide messages to blood vessels and vaginal submucosal glands. The actual sensory innervation of the vagina is marginal and must be studied by different methods other than an S100 stain at low power. The individual nerve fiber receptors in the mucosa need to be assayed under standardized conditions with a PGP 9.5 stain and compared against pain-free control patients who have had their meshes removed for other reasons. My interpretation of these figures is that the S100 stain is demonstrating a normal distribution of fascicles of autonomic motor nerves in the vaginal submucosa. The lack of association with the underlying polypropylene threads is also noted.

Figure set 7d. "Interposition of nerves, scar and damaged striated muscle in the mesh-scar plate, S100, 10x"

Figure set 7e. "Interposition of nerves, scar and damaged striated muscle in the mesh-scar plate, S100, 10x"

Figure set 7f. "Interposition of nerves, scar and damaged striated muscle in the mesh-scar plate, S100, 4x."

McLendon response to 7d through 7f: The proximity and distribution of nerves to muscle in this location implicate a voluntary motor function. Of note, in 7e, the drawn in polypropylene thread in the upper left hand corner is inappropriately placed as the tissue exhibits obvious distortion by folding. This nerve is not abutting a polypropylene thread.

In summary, while Dr. Iakovlev has offered several hypotheses about the pathogenesis of pain in these patients who have had their prostheses removed, his knowledge of the neuropathology of pain transmitting fibers is weak and his studies lack scientific rigor or supporting data from the literature that can be used to test his hypotheses. Indeed, in his own publication, he states, "[a]t present, general human tissue interactions with the mesh are known, but we have an incomplete understanding of interactions specific to a mesh material and design as well as the pathophysiology of any complications." (Blaivas et al. 2015).

Dr. Iakovlev makes a tacit assumption that all nerve fibers surrounded by fibrous tissue are entrapped in scar and also mediate pain sensation. This is far from true. Individual nerve fibers are the wires over which signals that monitor and control the body's response to its environment, and a number of signals must be monitored for normal function as well as for safety. Biologically, groups of nerve fibers (fascicles) are encased in a variable amount of fibrous tissue called a perineurium, which varies in thickness (Midroni 1995). Also the nerve fibers in the pelvis as elsewhere, specialize according to the type of nerve signal they carry (Mundy 2005). Some nerve fibers only carry motor signals (signals to move) to peripheral targets (muscles). These motor signals make the bladder contract, hair follicles to stand up, or the muscles in the pelvis to move. Some fibers carry autonomic (automatic) motor signals that make blood vessels dilate, sweat glands secrete and mucous glands secrete. Some fibers do carry sensation signals back to the brain and spinal cord. Sensation signals are not all pain related, however. The so-called somatic sensibilities are divided into four major modalities: 1) discriminative touch, which is required to recognize the size, shape and texture of objects and their movement across skin; 2) proprioception, the sense of static position and movements of the limbs and body; 3) nociception, the signaling of tissue damage or chemical irritation typically (pain and itch); and 4) temperature, which of course is cold or warmth (Kandel 2000). Pain fibers are three-fold, mechanical, thermal, and so-called polymodal. In general, these can be lumped into two categories, slow deep burning pain and sharp pain (Kandel 2000). Deep burning pain is transmitted through C fibers, small, non-myelinated fibers (Kandel 2000). Activation of nerve fiber impulses is through receptors, specialized endings of nerves that detect specific stimuli.

The sensory receptors on the ends of abdominal visceral nerves are similar to those of pain receptors in the skin. The identification of the nerve receptor helps to identify the type of sensation transmitted (Kandel 2000). The identification of sensory fibers cannot be accomplished via S100 immunostains, which stain Schwann cells and perineurial cells, the normal non-nerve conducting cells that support the axonal functions.

Dr. Iakovlev has not excluded the fact that findings similar to all of the described "abnormalities" might not also exist in the majority of women with these vaginal meshes who are pain free. Further studies are required to investigate the association of histopathologic findings with pain in a scientifically rigorous, blinded fashion. Pathologists who have examined

this in suburethral slings have found no correlation between inflammation or fibrosis and pain (Hill 2015).

An understanding of the density and types of nerve receptors is critical to understanding the pathophysiology of pain and autonomic functions mediated by nerves. The understanding of the methodologies to identify these receptors and the morphologic features of these receptors are considered primary pieces of knowledge for a neuropathologist performing this type of evaluation. Dr. Iakovlev has failed to appreciate the differences between nerve fiber location and nerve receptor location. As a result, his opinions regarding pain causation are scientifically unreliable.

III. COMPENSATION

My rates for work in this case are $550/hour for record review, $650/hour for deposition, and $5,000/day plus expenses for court room testimony.

IV. REFERENCE LIST

Bendavid R, Lou W, Kock A, Iakovlev V (2014), 'Mesh-Related SIN Syndrome. A surreptitious irreversible neuralgia and its morphological background in the etiology of post-herniorrhaphy pain', International Journal of Clinical Medicine, 5, 799-810.

Blaivas, J. G., et al. (2015), 'Safety considerations for synthetic sling surgery', Nat Rev Urol.

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Smith, T. M., et al. (2013), 'Pathologic evaluation of explanted vaginal mesh: interdisciplinary experience from a referral center', Female Pelvic Med Reconstr Surg, 19 (4), 238-41.

Svenningsen, R., et al. (2014), 'Risk factors for long-term failure of the retropubic tension-free vaginal tape procedure', Neurourol Urodyn, 33 (7), 1140-6.

Vervest, H. A., Bongers, M. Y., and van der Wurff, A. A. (2006), 'Nerve injury: an exceptional cause of pain after TVT', Int Urogynecol J Pelvic Floor Dysfunct, 17 (6), 665-7.1

Please see Exhibit B for additional materials provided.

V. Testimonial History

The following is a list of all other cases in which I have testified as an expert at trial or by deposition in the last four years:

Edens v. Wehman (Miami, FL): 9/9/11 (Deposition)
State of Georgia v. Oliver (Atlanta, GA): 2/2/12 (Hearing for Retrial Motion)
Lawrence v. Weddle (Lewisville, TX): 3/9/12 (Deposition)
State of California v. Cornejo (San Diego County, CA): 3/15/13 (Trial)
Liptak v. Rudolph, Dickinson, Alidina, et al (Tampa, FL): 2/4/14 (Deposition)
Thomas v. Emory Clinic (Atlanta, GA): 10/20/14 (Deposition)
Mullins v. Ethicon (Charleston, WV): 9/29/15 (Deposition)

State of North Carolina vs. Jason Moore (Gastonia, NC): 2/29/16 (Trial)

Date: March 1, 2016

Roger McLendon, M.D.